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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/591,447	06/09/2000	Steven Neville Chatfield	KCO1003US	4359

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EXAMINER	
HINES, JANA A	

ART UNIT	PAPER NUMBER
1645	19

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Applicati n No.	Applicant(s)	
	09/591,447	CHATFIELD ET AL.	
	Examin r	Art Unit	
	Ja-Na A Hines	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the c rrespondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19/2/03* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,7-17,20,25,27 and 31-41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,7-17, 20, 25, 27 and 31-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Amendment Entry

1. The amendment filed February 19, 2003 has been entered. Claims 2-6, 21-24, 26 and 28-30 have been cancelled. Claims 1, 7-17, 20, 25 and 27 have been amended. Claims 31-41 have been added. Claims 1,7-17, 20, 25, 27 and 31-41 are under consideration in this office action.

Withdrawal of Rejections

2. The following rejections have been withdrawn:

a) The rejection of claim 2-17 and 20-30 under 35 U.S.C. 112, second paragraph;

b) The scope of enablement rejection of claims 1-17 and 20-30 under U.S.C. 112, first paragraph; and

c) The rejection of claims 1-6, 11, 12-14, 21 and 30 under 35 U.S.C. 102(b) as being anticipated by Lazar et al (1996).

New Grounds for Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1,7-17, 20, 25, 27 and 31-41 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Neither the specification nor originally presented claims provides support for a composition comprising a pathogenic bacterium attenuated by a non-reverting mutation in the surA gene and carrier.

Applicant did not point to support in the specification for a composition comprising a pathogenic bacterium attenuated by a non-reverting mutation in the surA gene and carrier. Moreover, applicant failed to specifically point to the identity or provide structural characteristics of a composition comprising a pathogenic bacterium attenuated by a non-reverting mutation in the *surA* gene and carrier. Thus, there appears to be no teaching of a composition comprising a pathogenic bacterium attenuated by a non-reverting mutation in the *surA* gene and carrier. There is no support for a composition that distinguishes a composition comprising pathogenic or non-pathogenic bacteria. Applicant has not pointed to any pages within the instant specification or claims for support of the amendment and it appears that the entire specification fails to recite support for a composition comprising a pathogenic bacterium attenuated by a non-reverting mutation in the *surA* gene and carrier. Therefore, it appears that there is no support in the specification. Therefore, applicants must specifically point to page and line number support for the identity a composition

comprising a pathogenic bacterium attenuated by a non-reverting mutation in the surA gene and carrier as recited by the newly added amendments. Therefore, the new claims incorporate new matter and are accordingly rejected.

4. Claims 1,7-17, 20, 25, 27 and 31-41 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The claims are drawn to a composition comprising a pathogenic bacterium attenuated by a non-reverting mutation in a surA gene and a pharmaceutically acceptable carrier. However the instant specification does not provide for any undefined mutations within the bacterium. Claim 10 states that the composition comprises a mutation in the surA gene that is defined, thereby stating that the other mutations are not defined. The written description, in this case, only sets forth defined mutations inserted in the *sur*A gene that promotes folding of periplasmic proteins ompA, ompF and lamB; and therefore the written description is not commensurate in scope with the claims drawn to a composition comprising an attenuated pathogenic bacterium comprising undefined mutations.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the

'written description' inquiry, *whatever is now claimed.*" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116). Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115).

Thus, the structure of the undefined mutations comprised within the attenuated bacterium is not defined. With the exception of an attenuated mutant such as *Salmonella enteritidis* wherein the transposon was inserted in the *sur*A gene comprising a defined mutation, the skilled artisan cannot envision the detailed structure of the comprised bacterium, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of producing said bacterium. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The composition itself, along with the recited defined mutations and limitations are required.

Furthermore, In *The Reagents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement that defines a genus by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of examples, falling within the scope of the claimed genus. At section B(1), the court states that an adequate written description

requires a precise definition, such as by structure, formula, chemical name, or physical properties, not a mere wish or plan for obtaining the claimed chemical invention.

Therefore a precise description of defined mutation that creates a composition comprising an attenuated bacterium is necessary. However, no disclosure, beyond the mention of an attenuated mutant of *Salmonella enteritidis* wherein the transposon was inserted in the *sur*A gene that promotes the folding of particular periplasmic proteins and further comprising heterologous antigens such as the protective fragment C domain of tetanus toxin, also known as BRD115 is made in the specification, as described in the examples. This is insufficient to support the generic claims of a composition comprising a pathogenic bacterium attenuated by a non-reverting undefined mutation in the surA gene as provided by the Interim Written Description Guidelines published in the June 15, 1998 Federal Register at Volume 63, Number 114, pages 32639-32645.

Therefore only a composition comprising an attenuated mutant of *Salmonella enteritidis* wherein the transposon was inserted in the *sur*A gene with defined mutation and further comprising heterologous antigens such as the protective fragment C domain of tetanus toxin, also known as BRD115 as made in the specification and described in the examples of the specification, but not the full breadth of the claims meets the written description provision of 35 USC 112, first paragraph.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 1,7-17, 20, 25, 27 and 31-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lazer et al., (1996) in view of Dougan et al (US patent 5,527,529).

Lazar et al., disclose attenuated *E.coli* bacterium comprising a mutation in the surA gene. The SurA assists the folding of *E.coli* outer membrane proteins. SurA is a periplasmic protein of *E. coli* that has sequence similarity to the prolyl isomerase parvulin (abstract). SurA is cytoplasmic peptidyl prolyl isomerase from *E. coli* (page 1770). The authors determined that efficient folding of three outer membrane proteins requires SurA in vivo, thus the authors concluded that *surA* assists in the folding of certain secreted proteins, *ompA, ompF* and *lamB* but not in four other periplasmic proteins (abstract). The authors constructed a *surA* deletion to avoid the appearance of revertants of the *surA* allele (page 1770). The colony of bacterial cultures comprising *SurA* mutants was grown in rich medium (page 1770). However Lazar et al., do not teach using attenuated pathogenic bacteria in vaccines and compositions.

Dougan et al., (US Patent 5,527,529) teach vaccines and compositions comprising attenuated *Salmonella* having mutations in the outer membrane proteins. Attenuated bacteria are preferably gram-negative bacteria that colonize the mucosal

surface such as *Salmonella* and *Escherichia* (col. 2 lines 27-33). The attenuated microorganisms can be used in vaccine preparations or pharmaceutical compositions mixed with a pharmaceutically acceptable carrier (col. 2 lines 41-45 and col. 4 lines 24-29). The inventors found it possible to attenuate pathogenic bacteria by introducing a mutation into genes that are concerned with the regulation of one or more other genes (col. 1 lines 60-65). The attenuated bacterium can harbor mutations in *aroA, aroC* or *aroD* genes (col. 2 lines 55-59). The mutations can also occur in the *ompR* gene (col. 2 lines 3-6). The inventors teach methods for generating non-reverting mutations (col. 3 lines 5-17). Moreover the bacterial strains can be genetically engineered so as to express antigens from one or more different pathogens including fragment C from tetanus toxin (col. 3 lines 46-58). The inventors also teach a method for orally and intravenously administering the composition to mice and invoking an immune response, see examples 5 and 6. However Dougan et al., do not disclose a composition comprising a mutation of the *surA* gene.

Therefore, it would have been prima facie obvious at the time of applicants' invention to modify the pathogenic bacteria comprising a mutation in the surA gene as taught by Lazar et al., to further include mutations in one or more outer membrane regulation genes as taught by Dougan et al., who already teach that bacteria comprising such mutations was well known in the art and no more than routine skill would have been required to produce said attenuated bacteria. No more than routine skill would have been required at the time of applicants' invention to have used well-known

compositions and well known methods of invoking an immune response comprising attenuated comprising well-known mutations in pathogenic gram-negative bacterium that may be genetically altered to achieve well-known results. Moreover, one would have a reasonable expectation of success in mutating attenuated bacterium since the prior art already teaches mutations in genes which control outer membrane proteins.

Conclusion

6. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ja-Na Hines whose telephone number is

703-305-0487. The examiner can normally be reached on Monday-Thursday and alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on 703-308-3909. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Ja-Na Hines
April 29, 2003

LYNETTE R. F. SMITH
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600